AF

PATENT
Docket MZ 100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of: MICHAEL A. ZASLOFF

Serial No. 10/053,299 Examiner: Sheikh, Humera N.
Filed: 01/17/2002 Art Unit: 1615
Title: METHODS AND COMPOSITIONS FOR BLOCKING MICROBIAL ADHERENCE TO EUKARYOTIC CELLS

CERTIFICATE OF MAILING

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Signature of certifier

Henry E. Millson, Jr.
Typed or printed name of certifier

APPEAL BRIEF TRANSMITTAL

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Appellant's appeal brief, in triplicate, is transmitted herewith in accordance with 37 CFR 1.192.

Serial No. 10/053,299
Art Unit: 1615

The required small entity fee of One Hundred Sixty Five Dollars ($165.00) is enclosed.

Respectfully submitted,

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PATENT

Docket MZ 100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re: Application of: MICHAEL A. ZASLOFF

Serial No. 10/053,299 Examiner: Sheikh, Humera N.
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BRIEF ON APPEAL UNDER 37 C.F.R.§ 1.192

Commissioner for Patents
P.O.Box 1450
Alexandria, Va. 22313-1450

Sir:

REAL PARTY IN INTEREST

The real party interest is Innate Immunity Incorporated, a Delaware Corporation having a place of business at 311 Sumneytown Pike, Suite 2F, North Wales, Pa. 19454-2533.

RELATED APPEALS AND INTEREFERENCES

None.

STATUS OF CLAIMS

The claims in the application are claims 1-40. The claims on appeal are claims 1-16,18,25,31,32 and 34. Nonelected claims 17,19-24,26-30,33 and 35-40 have been cancelled as required by the Examiner. The claims on appeal have been rejected under 35 U.S.C. 103(a) as being unpatentable over the Sundstrom et al patent (U.S.6,388,056B1).

STATUS OF AMENDMENTS

Claims 1 and 25 have been amended and the above nonelected claims cancelled by a 37 C.F.R. Sec. 1.116 amendment dated 8/24/04. Accordingly, the claims on appeal set forth in the APPENDIX include the amendments to claims 1 and 25, since the Advisory Action dated 09/23/2004 indicated that the amendment dated 08/24/04 will be entered for purposes of appeal.

SUMMARY OF THE INVENTION

The present invention relates to methods for blocking the adherence of microorganisms to epithelial cells and other eukaryotic cells by applying isoleucine to the surface of the cells, i.e. this invention relates to a method for preventing or treating microbial infections by the application or administration of a composition containing isoleucine.

The invention also relates to compositions containing at least one isoleucine compound for applying to the above cell surfaces.

ISSUES

1. Are the claims on appeal obvious per se over the teachings of the Sundstrom reference?
2. If the Board finds the answer to issue no. 1 in the affirmative, has Appellant successfully rebutted any such presumption of obviousness?

GROUPING OF THE CLAIMS

The claims do not all stand or fall together, since independent claims 1 and 11 are, respectively, a method claim and a composition claim, and the dependent claims contain additional limitations not disclosed by the Sundstrom reference.

ARGUMENT

Before discussing the Examiner's rejections of the claims on appeal, the substantive sections of the Final Rejection dated 06/30/2004 and the Advisory Action dated 09/23/2004 relating to the rejected claims are set forth below as a basis for discussion and to make certain that Appellant does not in any way misrepresent the Examiner's position.

FINAL REJECTION DATED 06/30/2004

"Claims 1-16,18,25,31,32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sundstrom et al. (US Pat. No. 6,388,056 B1).

Sundstrom et al. teach compounds and methods for the prevention and treatment of microbial infection of a mammalian host through the administration of substrates for transglutaminases or antibodies against such substrates that inhibit the trangluatinase-mediated interaction with the mammalian host. These compounds and methods may be used in the identification, prevention or treatment of microbial infection of mammalian hosts, such as, for example, immunocompromised or immunosupressed humans. (see Abstract and col. 1, lines 1-15). The polypeptides used in the invention act as substrates for mammalian transglutaminases and include amino acids of *isoleucine,* serine and glutamine, whereby the amino acid residues are preferred to be in the L isomeric form, however, the D isomeric form may also be used (col. 9, lines 5-col. 10, line 11).

Sundstrom teach that during initial infection, the interaction of a microorganism with its mammalian host can include attachment or adhesion to the host cell surface, invasion of host cells, and elaboration of toxins. In certain instances, this interaction can be nonspecific. In others, such microbial interaction involves the specific binding of the microorganism to a particular receptor or receptor complex expressed on the host cell surface (col. 1, lines 20-32).

According to Sundstrom et al., the antibody is capable of inhibiting the interaction of a microrganism with a mammalian cell. The mammalian cell is a human cell, preferably a mucosal epithelial cell and most preferably a buccal epithelial cell (col. 4, lines 20-50).

At column 8, lines 34-52, Sundstrom et al. teach that in a preferred embodiment, a substrate for mammalian transglutaminases can inhibit the binding of one or more mammalian transglutaminases to purified Hwp1 protein or a polypeptide comprising the amino acid sequence of Fig. 1, wherein said polypepetide is itself capable of acting as a substrate for mammalian transglutaminases. In addition, microbial interaction with a mammalian host can include attachment or adhesion to the host cell surface, invasion of host cells, and elaboration of toxins, for example. The involvement of pathogenic mechanisms or virulence factors of the microorganisms can result in beneficial effects to the mammalian host.

In Example 7, cols. 19 and 20, Sundstrom *et al*: teach a pharmaceutical composition containing polypeptide substrates for mammalian transglutaminases in powder form, along with pharmaceutical carriers, which could also be prepared as a liquid preparation suitable for injection, for the purpose of inhibiting transglutaminase-mediated microbial interaction with a mammalian host. The peptides may be delivered by any convenient means that will result in the delivery to the subject of an effective amount to inhibit transglutaminase-mediated microbial interaction with a mammalian host. The amount administered will depend on the activity of the particular compound

administered, which may be readily determined by one skilled in the art.

It is the position of the Examiner that the prior art teaches the generic concept of the use of isoleucine to inhibit microbial infection and interaction with the mammalian host, since isoleucine is within the group of polypeptides disclosed at columns 10 and 16. One of ordinary skill would recognize that since isoleucine is taught to inhibit microbial interaction, it also teaches the prevention of the adherences of microbes, as desired by the applicant. Hence, no significant distinction is observed between the prior art and the instant invention.

With regards to the instantly claimed amounts and ranges of isoleucine employed, it is deemed obvious to one of ordinary skill in the art that suitable amounts and ranges could be determined through the use of routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters.

RESPONSE TO ARGUMENTS

Applicant's arguments filed 2/13/04 and 3/22/04 have been fully considered but they are not persuasive. Peptides may be delivered by any convenient means that will result in the delivery to the subject of an effective amount to inhibit transglutaminase-mediated microbial interaction with a mammalian host. The amount administered will depend on the activity of the particular compound administered, which may readily be determined by one skilled in the art.

It is the position of the Examiner that the prior art teaches the generic concept of the use of isoleucine to inhibit microbial infection and interaction with the mammalian host, since isoleucine is within the group of polypeptides disclosed at columns 10 and 16. One of ordinary skill would recognize that since isoleucine is taught to inhibit microbial interaction, it also teaches the prevention of the adherence of microbes, as desired by the applicant. Hence, no significant distinction is observed between the prior art and the instant invention.

With regards to the instantly claimed amounts and ranges of isoleucine employed, it is deemed obvious to one of ordinary skill in the art that suitable amounts and ranges could be determined through the use of routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters.

RESPONSE TO ARGUMENTS

Applicant's arguments filed 2/13/04 & 3/22/04 have been fully considered but they are not persuasive.

Firstly, the Applicant argued regarding Sundstrom et al. (US 6,388,056 B1)stating "Sundstrom's patent is directed to a long chain polypeptide containing isoleucine among a large number of other amino acids, all of which are set forth in a set fixed sequence in the polypeptide chain. There is no disclosure in Sundstrom of isoleucine itself.

Secondly, Sundstrom's polypeptide functions by a different mechanism, namely the prevention and treatment of microbial infection of a mammalian host through the administration of substrates for transglutaminases or antibodies against such substrates that inhibit the transglutaminase-mediated interaction of the microorganism with the mammalian host. There is no teaching of isoleucine itself or the teaching that isoleucine can function to block microbial adherence to the surfaces of eukaryotic cells. The only teaching by Sundstrom is with respect to the adherence of microbes to host cell surfaces, but not even a teaching that polypeptide can block such adherence by microbes. Isoleucine is not taught to inhibit microbial interaction as contended by the Examiner since Sundstrom contains no disclosure of isoleucine itself or the present discovery that isoleucine blocks microbial adherence to cell surfaces."

These arguments have been fully considered, but were not found to be persuasive. The instant claims are given their broadest interpretation consistent with the teachings of the specification. Applicant's specification and claims do not exclude the polypeptides or the amino acids defined in Sundstrom *et al.* When Applicant alleges that the term "consisting essentially of" excludes the presence of additional active ingredients, the burden is shifted to Applicant to show that the addition of polypeptides or amino acids is detrimental to the formulation.

The Applicant's argument that Sundstrom et al. utilizes a different mechanism from that instantly claimed is not persuasive since the particular mechanism is not relevant for the generic claims because Sundstrom et al. teach the use of isoleucine and teach a polypeptide composition comprising isoleucine. Applicant's claims merely require presence of isoleucine in a microbial blocking quantity. Additionally, Examiner notes that suggestions were made in the personal interview to further limit the term "microbial" in instant claim 1, since the term is very broad in that it includes various bacteria, viruses, yeast, fungi, etc. The term has not been further defined or limited, nor has any scientific data or clear evidence been presented showing that the claimed compound of Formula (1) treats all microbial organisms. The prior art teaches the same ingredients (i.e., isoleucine) for the same field of endeavor and to solve a similar problem as that desired by Applicants. Hence, the instant invention remains obvious and unpatentable over the prior art of record."

ADVISORY ACTION DATED 09/23/2004

"The request for reconsideration has been considered but does not place the application in condition for allowance because: The Applicant's argument that "there is no disclosure in Sundstrom of isoleucine itself' is not persuasive since the prior art teaches the use of isoleucine and teaches a polypeptide composition comprising isoleucine. Applicant's specification and claims do not exclude the polypeptides or the amino acids defined in Sundstrom. The argument that 'isoleucine is present as only 7 or 148 amino acids required to be present' is not persuasive since polypeptides or amino

acids would be detrimental to the formulation itself. Sundstrom expressly teaches isoleucine to inhibit microbial infection and interaction with the mammalian host."

Re: Issue No. 1

The present invention relates to compositions and methods limited to isoleucine and active isomers and analogs of isoleucine (see page 2, line 20-page 3, line 3 of the specification). The term "isoleucine" as used in the claims includes but is limited to the above. There are no polypeptides included in the term "isoleucine" as defined in the above section of the specification.

Moreover, all of the independent claims (1,11,18, and 32) are directed to compositions or compounds "consisting essentially of isoleucine".

With respect to the compounds used in the Sundstrom patent, these compounds are long chain polypeptides containing the chain SEQ.ID No.1, set forth in Figure 1. This chain contains the following amino acids linked together in the precise sequence shown in Fig. 1: serine, isoleucine, glutamine, phenylalanine, histidine, tryptophan, lysine, asparagine, leucine, glycine, threonine, aspartic acid, arginine, and alanine. Isoleucine comprises only seven of the 148 amino acids required in the sequence.

It is respectfully submitted that this polypeptide sequence does not fall within the term "composition (or compound) consisting essentially of isoleucine". The Sundstrom amino acid polypeptide sequence consists essentially of amino acids other than isoleucine.

Moreover, there is no disclosure in Sundstrom of isoleucine itself or active isomers or analogs of isoleucine to which the present claims are limited. The term

"isoleucine" does not include polypeptides containing isoleucine (which is present in the polypeptide as a reaction product with a large number of other amino acids).

There is no disclosure in Sundstrom of isoleucine itself, nor any compounds or compositions consisting essentially of isoleucine.

It is of course improper to rebuild a reference, in light of applicant's disclosure, in order for it to operate in a manner never intended or contemplated by the reference. Ex parte Garrett, POBA (1961) 132 USPQ 514. The reference, viewed by itself and not in retrospect, must suggest doing what applicant has done. In re Schaffer (CCPA 1956)) 108 USPQ 326; In re Skoll (CCPA 19975) 187 USPQ 481.

The Examiner contends in the Final Rejection that the prior art teaches the generic concept of the use of isoleucine, since isoleucine is within the group of polypeptides disclosed at columns 10 and 16. However, the teachings in columns 10 and 16 all refer to polypeptide sequences of linked amino acids, not isoleucine itself. Polypeptide sequences are not a "generic concept of the use of isoleucine", but rather a markedly different chemical entity containing small quantities of isoleucine as a reaction product with large quantities of other amino acids to form a precise linked sequence of amino acids. The isoleucine used in the present invention is not chemically linked with other amino acids, especially not in long chain polypeptides. It is not agreed that the prior art teaches the use of isoleucine to inhibit microbial infection and interaction with the mammalian host since only a long chain polypeptide, administered only by injection, was found to have this function.

In the "Response to Arguments", the Examiner contends that the present specification and claims do not exclude the polypeptides or the amino acids defined in Sundstrom. This contention is respectfully controverted. As discussed above, the specification limits the term "isoleucine" to isoleucine and active isomers and analogs of isoleucine (page 2, line 20-page 3, line 3). The present claims are so limited. The above terminology does not include polypeptide sequences.

The Examiner next contends that the burden is shifted to Applicant to show that the addition of polypeptides or amino acids is detrimental to the formulation. It is not agreed that Applicant has any such burden, since there is no case of prima facie obviousness that needs to be rebutted. It is respectfully contended that Appellant is not required by any patent law or practice to compare a claimed compound with an entirely different chemical entity in which the claimed compound is present as a reaction product, particularly where the presently claimed compound comprises a very small component of the disclosed reaction product (the reaction product being the reaction product of fourteen amino acids in which isoleucine is present as only 7 of 148 amino acids required to be present in a precise order in the polypeptide chain).

The Examiner also contends that the claimed amounts and ranges of isoleucine are obvious by the use of experimentation. However, since isoleucine itself is not disclosed by Sundstrom, this contention is respectfully submitted to be incorrect.

On page 7 of the Final Rejection, the Examiner refers to suggestions made in the personal interview to further limit the term "microbial" used in Claim 1. Appellant does

not agree that the term should be so limited; the claims as filed are directed to microbes broadly; and the operating examples show efficacy against bacterial microbial agents responsible for gingival infections, unknown microbial agents responsible for infectious diarrhea, those responsible for irritable bowel syndrome, and those responsible for bacterial vaginosis. In addition, the specification is broadly directed to reduction of microbial adherence to cell surfaces (see e.g. page 3, lines 7-13; page 4, lines 12-20; page 6, lines 19-20; etc.).

Concerning the Examiner's arguments with respect to the mechanism of action of Sundstrom's polypeptides, this is respectfully submitted to be irrelevant, since the compounds in the Sundstrom reference are not the isoleucine compounds of the present invention. Hence, the respective mechanisms of action are not relevant to the issue of patentability.

Moreover, the mechanism of action of the polypeptide in the Sundstrom patent is quite different from the mechanism of action of isoleucine in the present invention.

Sundstrom's invention relates to blocking an enzyme which causes microbes to remain stably attached to eukaryotic cells, i.e. the enzyme chemically crosslinks the microbes to the cell surface. Sundstrom uses a specific polypeptide to compete with bacteria as a substrate for the enzyme, competing with the bacteria by not allowing the bacteria to couple with the enzyme.

In the present invention, isoleucine blocks the binding of microorganisms to the cells by means of a single entity amino acid which exhibits no chemical activity, i.e. is

nonreactive and is chemically quite stable. Isoluceine does not react with enzymes. Isoleucine, when applied directly to cell surfaces, blocks the enzyme from coupling the surface of the cells to the microorganism.

It should also be noted that isoleucine is regarded by the FDA as a GRAS substance. This amino acid is a simple compound which is inexpensive, readily available, and which requires no synthetic preparative pathway, and can be administered orally or by direct application to cell surfaces. Sundstrom's polypeptide must be synthesized (fragmented from a fungal source). Also Sundstrom's polypeptide has unknown safety properties, and can be administered only by injection (if given orally, the polypeptide will be destroyed (digested) by stomach acids and enzymes).

It is submitted to be clearly unobvious to use isoleucine itself based on the teachings of Sundstrom of a long chain polypeptide in which very minor quantities of isoleucine are present.

The above discussion is applicable to all of the present claims. However, with respect to the dependent claims, claims 2-4 disclose microbial blocking quantities of isoleucine not disclosed by Sundstrom.

Claim 7 limits the composition to a pure powder of L(+) isoleucine and/or DL-isoleucine, clearly not disclosed by Sundstrom.

Claims 11-16,18,25,31,32 and 34 claim compositions comprising isoleucine and at least one additional pharmacologically active substance, also clearly not disclosed by

Sundstrom. Moreover, claims 14,16,31 and 34 are directed to formulations not disclosed by Sundstrom. Independent claim 1 and dependent claims 2-10 relate to a method for blocking microbial adherence to a eukaryotic cell surface by use of a composition consisting essentially of isoleucine present in a microbial blocking quantity. Sundstrom's polypeptide does not directly block microbial adherence to a cell surface but rather prevents bacteria from coupling with an enzyme that couples the bacteria to the cell surface, and Sundstrom does not disclose "a composition consisting essentially of isoleucine".

In the Advisory Action dated 09/23/2004, the Examiner contends that the prior art (Sundstrom patent) teaches the use of isoleucine. This statement is not correct. There is no disclosure of isoleucine itself in this reference, only a long chain polypeptide containing a small quantity of isoleucine. The Examiner further states that: "Sundstrom expressly teaches isoleucine to inhibit microbial infection and interaction with the mammalian host". It is respectfully contended that Sundstrom teaches no such thing, and the Examiner impliedly agrees since the rejection has been made under 35 U.S.C.103(a), and does not include a rejection under 35 U.S.C. 102.

Re: Issue No. 2

Even if the Board should find against Appellant with respect to Issue No. 1, it is submitted that Appellant has rebutted any presumption of prima facie obviousness.

In Example 1 on pages 15-17, patients with low grade gingival infection were treated with pure crystalline isoleucine powder applied directly to the gums. Gingival

scrapings taken prior to isoleucine use showed an average of at least 200 bacteria on each cell, plus definite signs of inflammation. After a 7 day treatment with isoleucine, 80% of the cells were completely free of bacteria, 15% had only 1-10 bacteria per cell, and only 5% were fully covered with adherent bacteria.

The above results were totally unexpected, and cannot be considered to be obvious from any teachings of the Sundstrom patent (especially since Sundstrom's polypeptide must be injected).

In Example 2 on pages 17-19, isoleucine was administered to treat infectious diarrhea. No medications were administered to the three patients having the infectious diarrhea. One individual was treated with oral isoleucine, six days after ingestion of the infectious agent, while the other two were continued on restricted diets. A reduction of stool frequency was noted with the isoleucine treated patient within 12 hours of initiation of isoleucine therapy. This reduction continued until the third day when no stools were passed. By day 4 a normal stool was passed and the diarrheal episode had passed.

The two patients not treated with isoleucine experienced diarrhea for 11 days after ingestion of the infectious agent.

The above results are unexpected and unobvious over any teachings of the Sundstrom reference, especially since the isoleucine was administered orally, which is not possible with a polypeptide.

In Example 3 on pages 19-20, isoleucine was administered orally to two patients having irritable bowel syndrome and a 20 year history of this problem.

Within 2 days after isoleucine administration, bloating, urgency to defecate, and gassiness had disappeared. The patients described their bowel function as "normal" for the first time in 20 years. They were maintained on isoleucine for one month with consistent response. Within 2 days after withdrawal from isoleucine, the former symptoms of irritable bowel syndrome returned.

The above results are unexpected, and unobvious over any teachings of the Sundstrom reference.

In Example 4 on page 20, isoleucine was administered locally to the vagina of a patient with symptoms of bacterial vaginosis associated with onset of menstrual cycle.

The isoleucine was self-administered twice a day. Within 2 days symptoms of vaginosis disappeared. Isoleucine therapy was continued for several days following termination of menstrual cycle and then stopped. Isoleucine was again administered during the following months, and based on the symptoms and signs, the vaginosis appeared to be been effectively cured.

These results are unexpected, and are unobvious over any teachings of the Sundstrom reference.

In light of the above four Examples, it is respectfully contended that any assumption of prima facie obviousness has been successfully rebutted.

The Board is respectfully requested to find for Appellant with respect to both issues, and to find the claims on appeal patentable over the Sundstrom reference.

Respectfully submitted,

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APPENDIX

CLAIMS ON APPEAL

1. A method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying to said surface a pharmacologically acceptable composition consisting essentially of isoleucine present in a microbial blocking quantity.
2. The method of claim 1 wherein the microbial blocking quantity is in the range of from about 0.1 ug/cm^2 to about 1 gm/cm^2 of eukaryotic cell surface area.
3. The method of claim 2 wherein said quantity is from about 3 ug/cm^2 to about 100 ug/cm^2 .
4. The method of claim 2 wherein said quantity is from about 10ug/cm^2 to about 100ug/cm^2.
5. The method of claim 1 wherein the mammal is man.
6. The method of claim 1 wherein the epithelial surface is one or more of the oral cavity, GI tract, respiratory tract, genitourinary tract, skin, eye, and vaginal/cervical area.
7. The method of claim 1 wherein the composition consists of a pure powder of L(+)-isoleucine and/or DL-isoleucine.
8. The method of claim 1 wherein the composition is in the form of a dry powder, a paste, a solution, a gel, a tablet, a lozenge, or a capsule.

9. The method of claim 1 wherein the composition is directly applied to the epithelial said surface.

10. The method of claim 1 wherein the composition is in the form of a pharmacologically acceptable aqueous composition containing from about 0.01 ug/ml to about 50ug/ml of isoleucine.

11. A pharmacologically acceptable composition comprising:

    A) from about 0.001 to about 99% by weight of a compound consisting essentially of isoleucine;

    B) at least one additional pharmacologically active substance; and, optionally,

    C) pharmacologically acceptable carrier materials and/or excipients.

12. The composition of claim 11 wherein component A) is present in from about 0.002 to about 50% by weight.

13. The composition of claim 11 wherein component A) is present in from about 0.1 to about 25% weight.

14. The composition of claim 11 wherein said composition is in the form of a dental care product.

15. The composition of claim 14 wherein component B) is one or more of a fluoride, xylitol, an antibody, and an anti-microbial agent.

16. The composition of claim 14 wherein the composition is in the form of a toothpaste or a gel.

17. A toothpaste or gel comprising a eukaryotic cell surface blocking quantity of a compound consisting essentially of isoleucine.

25. The composition of claim 11 wherein component B) is an antifungal and/or antimicrobial substance.

31. The composition of claim 11 wherein the composition is in the form of a wound ointment or cream, and component B) is one or more of an antimicrobial substance and an anesthetic.

32. A would ointment or cream comprising a eukaryotic cell surface blocking quantity of a compound consisting essentially of isoleucine.

34. The composition of claim 11 wherein the composition is in the form of a skin ointment or cream.